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AUTHOR(S):

Togashi, Yosuke; Masago, Katsuhiro; Hamatani, Yasuhiro; Sakamori, Yuichi; Nagai, Hiroki; Kim, Young Hak; Mishima, Michiaki

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Successful erlotinib rechallenge for leptomeningeal metastases of lung adenocarcinoma after erlotinib-induced interstitial lung disease. A case report and review of the literature

Authors:

Yosuke Togashi *, Katsuhiro Masago, Yasuhiro Hamatani, Yuichi Sakamori, Hiroki Nagai, Young Hak Kim, Michiaki Mishima

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan

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*** Corresponding author:**

Yosuke Togashi, M.D.

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan.

Tel: +81-75-751-3830; Fax: +81-75-751-4643

18 E-mail: ytogashi@kuhp.kyoto-u.ac.jp

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Abstract

The most serious adverse reaction associated with treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is drug-induced interstitial lung disease (ILD). Because EGFR-TKIs are key drugs for patients with non-small cell lung cancer who have somatic activating mutations of the epidermal growth factor receptor gene (*EGFR* mutations), several cases of retreatment with EGFR-TKIs after ILD induced by these drugs have been reported. Here, we present a 68-year-old man with lung adenocarcinoma and leptomeningeal metastases having an *EGFR* mutation who was retreated with erlotinib after erlotinib-induced ILD. He suffered no ILD recurrence and his leptomeningeal metastases dramatically improved. In addition to the present case, reports of nine patients who were retreated with EGFR-TKIs after ILD were found in the literature. Only one patient had recurrence of ILD (although seven were retreated at a reduced dose of EGFR-TKIs, including the patient with recurrence). In contrast, three patients had no recurrence of ILD even without dose-reduction. These reports suggest that dose-reduction plays a limited role in preventing recurrence. Many patients received corticosteroids during retreatment, but not the one with recurrence of ILD. This may suggest that corticosteroids can prevent recurrence due to their

antiinflammatory properties.

Key words: epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, erlotinib, interstitial lung disease, rechallenge, epidermal growth factor receptor gene mutation, leptomeningeal metastases

1. Introduction

Because patients with non-small cell lung cancer (NSCLC) who have somatic activating mutations of the epidermal growth factor receptor (EGFR) gene (*EGFR* mutations) generally respond to EGFR-tyrosine kinase inhibitors (EGFR-TKIs; gefitinib or erlotinib) and can achieve long-term progression-free survival, the presence of *EGFR* mutations is a very useful marker for facilitating the choice of treatment for NSCLC [1-7]. Although systemic chemotherapy for leptomeningeal metastasis (LM) has been thought to play a limited role because of the belief that the brain is a pharmacologic sanctuary site, several studies have documented the effectiveness of EGFR-TKIs in the treatment of LM of NSCLC with *EGFR* mutations [8-10].

The most common adverse events associated with treatment with EGFR-TKIs are rash and diarrhea [11, 12]. Although not too frequent, the most serious adverse reaction is drug-induced interstitial lung disease (ILD) [13-16]. Because EGFR-TKIs are key drugs for patients with NSCLC having *EGFR* mutations, several cases of drug rechallenge after ILD induced by EGFR-TKIs have been reported. Here, we present a case report of a 68-year-old man with lung adenocarcinoma and LM having an *EGFR*

mutation who received erlotinib retreatment after erlotinib-induced ILD. No evidence of ILD recurrence was seen, and his LM dramatically improved. We also review the relevant published literature in this topic.

2. Case presentation

A 68-year-old Japanese man with a 40 pack-year history of smoking was diagnosed with stage IV lung adenocarcinoma (bone metastases). After one cycle of ~~carboplatin plus pemetrexed as~~ first-line cytotoxic chemotherapy, he suffered fatigue and electrolyte abnormality (both grade 3) as complications and elected to discontinue the~~se drugs~~ chemotherapy. *EGFR* mutational analysis revealed an exon 20 point mutation (L858R), and he therefore started erlotinib at 150 mg daily. Although he achieved a partial response (Fig 1A and 1B), he had cough and dyspnea on effort 8 weeks after initiation of erlotinib therapy. Chest computed tomography (CT) showed bilateral air space consolidations (Fig. 1C). Bronchoalveolar lavage (BAL) fluid contained no malignant cells and no pulmonary pathogens including bacteria, fungi, and Pneumocystis were identified. The fraction of lymphocytes in BAL fluid was

increased to 60%. Therefore, erlotinib-induced ILD (organized pneumonia [OP] pattern) was strongly suspected. Erlotinib was discontinued and 30 mg daily prednisolone (PSL) was initiated. Symptoms and bilateral consolidations in the CT improved, and PSL was gradually tapered to 5 mg (Fig. 1D).

After ~~cessation of erlotinib, he had received no treatment for 6 months because his lung cancer did not progress and he refused any further treatment. However; after~~ 6 months without treatment, he had headache and impaired consciousness, and his Eastern Cooperative Oncology Group performance status (ECOG PS) deteriorated to 2. Cerebrospinal fluid (CSF) testing revealed the presence of malignant cells and he was diagnosed with LM. He refused any cytotoxic chemotherapy; instead administration of 250 mg daily gefitinib and 4 mg daily betamethasone in addition to whole brain radiotherapy was initiated. His symptoms and CSF test, however, worsened, and his ECOG PS deteriorated to 4. The patient requested erlotinib retreatment despite the risk of ILD, so we initiated administration of 150 mg daily erlotinib together with 4 mg betamethasone. Soon after initiation of erlotinib, his symptoms dramatically improved and ECOG PS improved to 1. Both his CSF test and brain magnetic resonance imaging also improved (Fig. 2). His LM has not worsened for 8 months of erlotinib rechallenge.

During the period, betamethasone was gradually tapered to zero and ILD recurrence has not been observed.

3. Literature review

In addition to the present case, a literature search identified a total of nine cases who received EGFR-TKI retreatment after ILD induced by these drugs (Table 1) [17-24]. Three received gefitinib after gefitinib-induced ILD [17, 18, 24], 5 were treated with erlotinib after gefitinib-induced ILD [19-22], and the remaining one (two including the present case) received erlotinib after erlotinib-induced ILD [23]. Two patients were Asians and the other reports were also from Asia, but the ethnicity of the patients was not stated. Six patients were never-smokers and m~~M~~any had severe ILD as revealed by bilateral diffuse ground glass opacities (GGO) on CT. ILD of all patients went into remission on cessation of EGFR-TKIs and initiation of corticosteroid therapy. Two patients (cases 2 and 10 in Table 1) could not be given any chemotherapy other than EGFR-TKIs due to their poor PS. Although the others were fit enough to receive chemotherapy, they requested EGFR-TKIs again instead. During the EGFR-TKI

rechallenge, only case 3 suffered recurrence of ILD. Seven patients were retreated with a lower dose of EGFR-TKIs including case 3 who nonetheless recurred. In contrast, cases 5, 6, and 10 had no recurrence in spite of receiving 150 mg daily erlotinib. Many patients were given corticosteroids during EGFR-TKI rechallenge, but not case 3. However; case 2 also received no corticosteroids but did not recur.

4. Discussion

In this article, we presented a case of successful erlotinib rechallenge for LM after erlotinib-induced ILD and have summarized previous similar reports (Table 1). Although nine of these ten cases successfully rechallenged with EGFR-TKIs without the recurrence of ILD, most of the cases that do suffer recurrence might simply not be reported. Therefore, the risk of ILD should be considered whenever reinitiating EGFR-TKI treatment after ILD induced by these drugs. Eight of these ten cases could have received other chemotherapies, but the patients requested EGFR-TKI therapy again despite their awareness of the risk of ILD. This was permissible because the efficacy of EGFR-TKIs was predicted from *EGFR* mutations or previous tumor

response. Our case (case 10 in Table 1) was not eligible for other chemotherapy due to his poor PS, and the treatment of choice remained erlotinib or best supportive care. Several cases in which LM resistant to gefitinib were improved by erlotinib due to its higher CSF concentration have been reported [25-27] and ILD with an OP pattern on CT seems to be associated with good prognosis [28]. Therefore, we used 150 mg daily erlotinib because of its expected clinical benefit and efficacy despite the risk of ILD.

Seven patients were retreated with lower doses of EGFR-TKIs. Three received a lower dose of erlotinib after gefitinib-induced ILD. However, the area under the curve (AUC) of serum concentration of erlotinib at the approved dose (150 mg daily) is 7 times larger than gefitiinib at the approved dose (250 mg daily) [29]. Therefore, in spite of dose-reduction, higher AUC could be achieved by erlotinib than gefitinib in these patients. In addition, case 3 had recurrence of ILD despite dose-reduction, and three cases (cases 4, 5, and 10) had no recurrence of ILD although they received 150 mg daily erlotinib. From these findings, we speculate that blockade of the EGFR signaling pathway by EGFR-TKIs is not necessarily associated with the occurence of ILD and that EGFR-TKI dose-reduction plays only a limited role in preventing recurrence.

Dallas et al. have reported a similar case of successful erlotinib rechallenge after erlotinib-induced ILD (case 9). As with the case reported here, that patient had also received erlotinib retreatment together with corticosteroid after erlotinib-induced ILD. Many cases were also given corticosteroids together with the EGFR-TKIs, resulting in clinical benefit. In contrast, case 3 had recurrence of ILD without administration of corticosteroid. This is consistent with the general use of corticosteroids for treating drug-induced ILD [30, 31]. Thus, corticosteroid can prevent the recurrence of ILD, probably because of its antiinflammatory action.

Six patients were never-smokers and CT finding of many patients revealed bilateral diffuse GGO. We can predict the recurrence of ILD from these factors. In fact, a previous report has shown that smoking status is one of the risk factors for ILD [14]. In contrast, another report has shown that the incidence of the bilateral GGO pattern on CT was relatively high and that such patients have high mortality rate [28]. Therefore, great caution is required when undertaking rechallenge in these patients.

The mechanism responsible for ILD induced by EGFR-TKIs remains unclear and several instances of successful EGFR-TKI rechallenge after ILD have been reported, as described above. EGFR-TKIs are key drugs for patients with NSCLC having *EGFR*

mutations. Therefore, rechallenge after ILD should be undertaken considering the balance between risk and benefit. This present case had an *EGFR* mutation and was not eligible for other chemotherapy due to his poor PS. Therefore, the treatment of choice remained erlotinib or best supportive care. Although he recognized the risk of ILD, he requested erlotinib retreatment, and this was successful. From these findings, we suggest 3 criteria before deciding on EGFR-TKI rechallenge after ILD; a) The patient has an *EGFR* mutation. b) Few other treatment options except EGFR-TKI remain. c) The patient recognizes the risk of ILD and makes an informed decision to go ahead with the rechallenge. In order to assess the safety and the risk of this approach, more similar cases including other ethnicities need to be accumulated and, if ethically possible, prospective studies in patients who meet these criteria should be performed~~are required~~.

Conflict of interest statement

None declared.

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310 **Figure Legends**

311

312 Figure 1. Chest computed tomography (CT) in a 68-year-old man. A: CT scan before

313 erlotinib treatment showing a mass in the left upper lobe. B, C: CT scan 10 weeks after

314 initiation of erlotinib treatment showing a decreased mass (B), but visible bilateral air

315 space consolidations (C). D: Eight weeks after cessation of erlotinib and initiation of

316 corticosteroid, showing improvement of the bilateral air space consolidations.

317

318 Figure 2. Brain magnetic resonance imaging (MRI). A: Contrast

319 (gadolinium)-enhanced T1-weighted MRI during gefitinib treatment before erlotinib

320 rechallenge, revealing leptomeningeal metastases (arrowheads). Patient performance

321 status (PS) had deteriorated to 4. B: Two weeks after the initiation of erlotinib, showing

322 improvement of the leptomeningeal metastases. PS also improved to 1.

Table 1. Patient characteristics

Case	Age (yr)	Sex	Ethnicity [a]	Histology	*EGFR* status	Smoking status	Onset of ILD	Cause of ILD (dose)	CT of ILD	Respiratory condition [d]	Treatment for ILD
1	62	F	NA	Ad	NA	Never	13 months	Gefitinib (125 mg/day [b])	NA [c]	NA	Cessation and corticosteroid
2	56	M	NA	Ad	Exon 21; L858R	15 pack-year	45 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
3	59	M	NA	Ad	Wild type	60 pack-year	23 days	Gefitinib (250 mg/day)	Diffuse GGO	PaO_2, 46.9 mmHg	Cessation and corticosteroid
4	28	F	NA	Ad	Exon 19 deletion	Never	28 days	Gefitinib (250 mg/day)	Diffuse GGO	Need nasal oxygen	Cessation and corticosteroid
5	62	M	NA	Ad	Exon 19 deletion	18 pack-year	24 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
6	62	M	NA	Ad	NA	Never	6 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 84%	Cessation and corticosteroid
7	77	F	NA	Ad	NA	Never	7 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 93%	Cessation and corticosteroid
8	41	F	NA	Ad	NE	Never	20 days	Gefitinib (250 mg/day)	Patchy air space consolidation	PaO_2 <45 mmHg	Cessation and corticosteroid
9	77	F	Asian	Ad	Exon 19 deletion	Never	5 weeks	Erlotinib (150 mg/day)	Diffuse GGO	Oxygen saturation, 92%	Cessation and corticosteroid
10	68	M	Asian	Ad	Exon 21; L858R	40 pack-year	8 weeks	Erlotinib (150 mg/day)	OP pattern	PaO_2, 78.6 mmHg	Cessation and corticosteroid

F, female; M, male; *EGFR*, epidermal growth factor receptor gene; ILD, interstitial lung disease; CT, computed tomography; GGO, ground glass opacity; OP, organized pneumonia; PaO_2, arterial oxygen pressure; NA, not available; NE, not evaluated.

[a] The ethnicity of eight cases was not available, but all reports were from Asia.

[b] Gefitinib was administered every other day due to blepharitis.

[c] Case 1 had alveolar hemorrhage.

[d] There was no description of actual PaO_2 or oxygen saturation in Cases 2, 4 and 5. But Cases 2 and 5 had severe ILD and Case 4 needed nasal oxygen supplementation (1 L/minute). Case 9 was supported by mechanical ventilation.

Table 1. Continued

Case	ECOG PS (symptoms)	Period between EGFR-TKIs	Rechallenge (dose)	Corticosteroid during rechallenge	Recurrence of ILD	Response of initial/rechallenge	References
1	1	12 months	Gefitinib (125 mg/day [e])	NA	No	SD/SD	[17]
2	NA (Severe dyspnea and confined to bed)	5 months	Gefitinib (125 mg/day)	No	No	PR/PR	[18]
3	NA (General fatigue)	3 months	Gefitinib (Intermittent [f])	No	Yes	NA	[19]
4	NA (Dyspnea)	4 months	Erlotinib (50 mg/day)	Yes → tapered	No	PR/PR	[20]
5	NA (Neurological symptoms)	3 months	Erlotinib (150 mg/day)	NA	No	NA/PR	[21]
6	NA	6 days	Erlotinib (150 mg/day)	Yes	No	PR/PR	[22]
7	NA	6 weeks	Erlotinib (100 mg/day)	Yes	No	PR/PR	[22]
8	NA	NA (about 6 months)	Erlotinib (75 mg/day)	Yes → off	No	PR/PR	[23]
9	NA	10 days	Erlotinib (100 mg/day)	Yes → off	No	PR/NA	[24]
10	4 (Impaired conscious)	7 months	Erlotinib (150 mg/day)	Yes → off	No	PR/PR	Present case

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; SD; stable disease; PR, partial response.

[e] Gefitinib was administered every other day.

[f] Gefitinib (250 mg daily) was administered for 7 days followed by 2 weeks rest.

Figure 1

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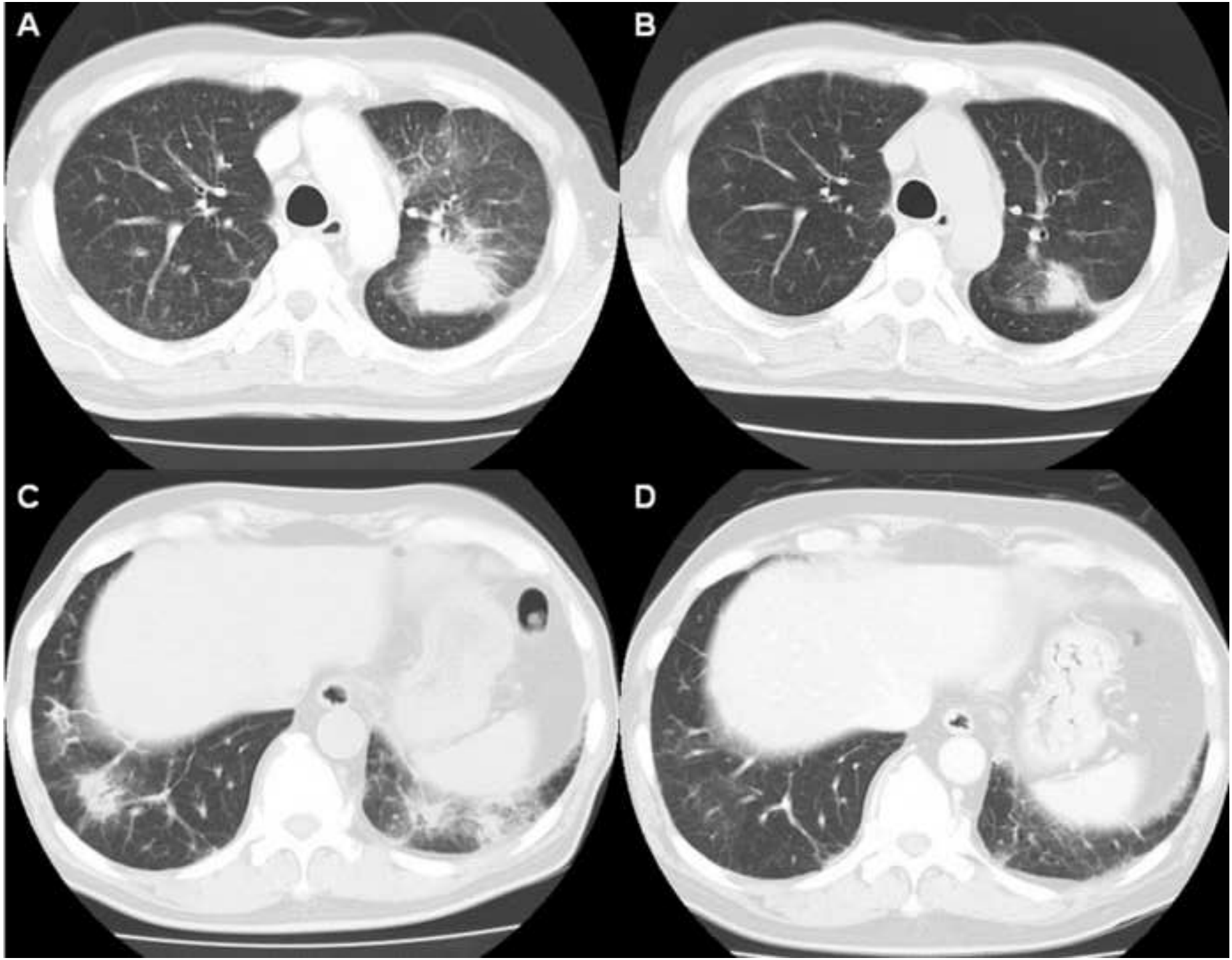

Figure 2

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